IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Maurizio Valleri & Alessandro Tosetti

Examiner : Pulliam, Amy E.

Serial No.: 09/463,586

Art unit : 1615

Filed : April 24, 2000

For : PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D, THEIR PREPARATION AND THERAPEUTIC USE

DECLARATION UNDER 37 CFR 1.132

I, Maurizio VALLERI, declare that:

1. I am an Italian citizen residing in Florence ITALY

2. I am familiar with the English language.

3. I further declare that:

I graduated in Pharmaceutical Chemistry and Technology at the University of Florence, Italy, in 1982. and have studied Industrial Pharmacy at the University of Pavia, Italy.

4. I have attended intensive professional courses in
"Pharmaceutical process development", Amsterdam 1996
"Pilot plant studies and process scaling", Amsterdam 1997
"Powders: their properties and processing"; Amsterdam 2003

5. At the present time, I am responsible for process transfer technology. in the galenic department of A. Menarini Manufacturing Logistics and Services, Florence Italy

6. I further declare the following experiments were carried out under my direct supervision: Sachets were prepared using the procedures disclosed in the above identified application where Vitamin D as Vitamin D3 800 IU and calcium phosphate in the amount of 3.1g ( corresponding to 1200 mg of calcium ion) were granulated using each of the polymeric binders set forth in Table 1; other excipients as indicated in the examples 1-2 disclosed in the above identified application, with the exception of tests 15-16 that follow the examples 3-4 of the same application. The experiments were performed in order to show that for the desired amounts of calcium phosphate and vitamin D, the traditional granulating process with water (the 'wet' method) or the modified method by Meignant (the 'wet/dry' method) are not feasible, and a process without water (the 'dry' method) is requested; for this dry method particular liquid binders which allow aggregation are necessary (the 'dry' aggregation method). The success of the process is evaluated on physical and organoleptic characteristics, such as granules quality, disintegration time, D3 content uniformity, and taste. Different amounts of polymers were used in each test, due to the different manufacturing method employed. The Vitamin D3 uniformity content is evaluated according to U.S. Pharmacopoeia.

TABLE 1

| Polymer used | Granulation Method | Amount (mg) / unit | Vit D3 Content uniformity | Evaluation |
|---|---|---|---|---|
| | | | USP reference | |

| | | | | |
|---|---|---|---|---|
| 1. polyvinyl pyrrolidone | Wet | 50 | ND | No granules formation<br>No flowability.<br>improvements |
| 2. polyvinyl pyrrolidone | Wet | 100 | OS | Some hard granules<br>No flowability.<br>improvements<br>Bad water dispersion<br>Sandy taste |
| 3. PEG 6000 | Wet | 500 | OS | Some hard granules<br>Bad water dispersion<br>Sandy taste |
| 4. Mannitol | Wet | 200 | OS | Hard granules<br>Bad water dispersion<br>Sandy taste |
| 5. Maltodextrin | Wet | 250 | OS | Hard granules<br>Bad water dispersion<br>Sandy taste |
| 6. Cellulose derivatives (HPMC) | Wet | 50 | ND | No granules formation<br>No flowability<br>improvements |
| 6. Cellulose derivatives (HPMC) | Wet | 100 | OS | Some hard granules<br>No flowability<br>improvements<br>Bad water dispersion<br>Sandy taste |
| 7. polyvinyl pyrrolidone | Wet/Dry (Meignant) | 80 | OS | Some hard granules<br>No flowability<br>improvements<br>Bad water dispersion<br>Sandy taste |
| 8. polyvinyl pyrrolidone | Dry | 100 | ND | No granules formation |
| 9. polyvinyl pyrrolidone | Dry | 200 | ND | No granules formation |
| 10. polyvinyl pyrrolidone | Dry | 500 | ND | No granules formation |
| 11. polyvinyl pyrrolidone | Dry | 1000 | ND | No granules formation |
| 12. PEG 6000 | Dry | 500 | ND | No granules formation |
| 13. | Dry | 500 | ND | No granules formation |

| Maltodextrin | | | | |
|---|---|---|---|---|
| 14. Wax | Dry Aggregation | 500 | OS | Some hard granules Bad water dispersion Greasy taste Unpleasant sol. appearance |
| 15. Silicon oil | Dry Aggregation | 500 | C | Good water dispersion Unpleasant sol. appearance |
| 16. Liquid paraffin | Dry Aggregation | 500 | C | Good water dispersion Unpleasant sol. appearance Slight unpleasant taste |
| 17. PEG 400 | Dry Aggregation | 800 | C | Good water dispersion Good sol. appearance Acceptable taste |
| 18. Propylene glycol | Dry Aggregation | 800 | C | Good water dispersion Good sol. appearance Acceptable taste |
| 19. Propylene glycol | Dry Aggrgation | 1000 | C | Good water dispersion Good sol. appearance Slight bitter |

ND: not determined OS: out of specification C: compliance

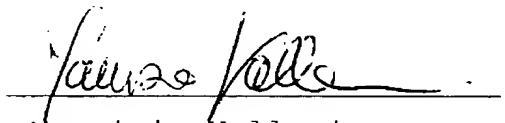
7.From the above results, it is apparent that: a) tests 1-6 do not provide a satisfactory granulation, b) test 7, performed according to the teachings of Meignant et al, gives unsatisfactory results, similar to that of tests 1-2, c) tests 8-13 show that solid binders, used with the dry granulating process, are not suitable for the amounts of Calcium and Vitamin D described in the above identified application, d) test 14 show that wax is not satisfactory, e) tests 15-19, which are according to the invention described in the above identified application, are satisfactory and provide granules with good dispersion in water. In addition, compositions 17-19 provide the best results in terms of appearance, water dispersion and taste. In conclusion the use of liquid ligands chosen (PEG 400, propylene glycol, etc.) give best results in term of granules quality, disintegration time, D3

content uniformity, and taste. Different amounts of polymers were used in each trial, due to the different manufacturing method employed.

8. I further declare that PVP is a classic binder in pharmaceutical industry. It is used principally in solvent (water or organic) granulation and bring to good granulates for tablet production. Remington's Pharmaceutical Sciences ( 20th Ed.) provides a general list of components that could be used for this application which include: sugars, synthetic and natural gums, cellulose derivatives, polyvinylpyrrolidone and mentions that "other agents may be considered binders under certain circumstances are Polyethylene glycol (PEG), waxes, …..". These "certain circumstances" are referred to higher-molecular weight PEG, i.e. a molecular weight more than 1,000, which are solid at room temperature. Use of these PEG types is limited because they can cause prolonged disintegration. Similarly solid high molecular weight PEG should be considered in the references by Andoh and Tovey. The use of low molecular weight (300-400) PEG as granulation agent for oral solid dosage forms is quite uncommon.

9. I further declare that all the statements of my own knowledge are true and that all the statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statement and the like so make are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Applicant or of any patent issuing thereon.

October, 27th 2005



Maurizio Valleri